

# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION

REC'D 01 APR 2005  
INTERNATIONAL PRELIMINARY EXAMINATION REPORT PCT

(PCT Article 36 and Rule 70)

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| Applicant's or agent's file reference<br>BIF023272/WO  | <b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416) |  |
| International application No.<br>PCT/EP 03/13695   | International filing date (day/month/year)<br>06.11.2003   | Priority date (day/month/year)<br>07.11.2002 |
| International Patent Classification (IPC) or both national classification and IPC<br>G01N33/50 |  |  |
| Applicant<br>GENODYSSEE et al.   |  |  |

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|---|
| <p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 8 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 2 sheets.</p>  |
| <p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> <li>I <input checked="" type="checkbox"/> Basis of the opinion</li> <li>II <input type="checkbox"/> Priority</li> <li>III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</li> <li>IV <input type="checkbox"/> Lack of unity of invention</li> <li>V <input checked="" type="checkbox"/> Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</li> <li>VI <input type="checkbox"/> Certain documents cited</li> <li>VII <input type="checkbox"/> Certain defects in the international application</li> <li>VIII <input type="checkbox"/> Certain observations on the international application</li> </ul> |

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| Date of submission of the demand<br>27.05.2004  | Date of completion of this report<br>01.04.2005                   |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office - P.B. 5818 Patentlaan 2<br>NL-2280 HV Rijswijk - Pays Bas<br>Tel. +31 70 340 - 2040 Tx: 31 651 epo nl<br>Fax: +31 70 340 - 3016 | Authorized Officer<br>Tuynman, A<br>Telephone No. +31 70 340-3741 |



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/13695

## I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

### Description, Pages

1-30 as originally filed

### Claims, Numbers

1-14 received on 14.02.2005 with letter of 14.02.2005

### Drawings, Sheets

1/3-3/3 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages:
- the claims, Nos.:
- the drawings, sheets:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP 03/13695

5.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).  
*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*
6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
  - the entire international application,
  - claims Nos. 1,3-13 (industrial applicability)  
because:
  - the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):
  - the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 14 (in part) are so unclear that no meaningful opinion could be formed (*specify*):  
**see separate sheet**
  - the claims, or said claims Nos. 14 (in part) are so inadequately supported by the description that no meaningful opinion could be formed.
  - no international search report has been established for the said claims Nos. 1,3-13 (industrial applicability)
2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
  - the written form has not been furnished or does not comply with the Standard.
  - the computer readable form has not been furnished or does not comply with the Standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

|                               |             |      |
|-------------------------------|-------------|------|
| Novelty (N)                   | Yes: Claims | 1-13 |
|                               | No: Claims  | 14   |
| Inventive step (IS)           | Yes: Claims | 1-13 |
|                               | No: Claims  | 14   |
| Industrial applicability (IA) | Yes: Claims | 2,14 |
|                               | No: Claims  |      |

**2. Citations and explanations**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP 03/13695

**see separate sheet**

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Present claims 14 relate *inter alia* to therapeutic agents or the use of such therapeutic agents defined by reference to a desirable characteristic or property, namely compounds being obtainable by the method according to any one of the claims 1 to 14.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a limited number of such therapeutic agents. In the present case, the claims so lack support, and the application so lacks disclosure. To select such therapeutic agents via a method used in claims 1-14, would require undue experimentation and therefore this claim is not allowable (Guidelines C-III, 4.7).

Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the therapeutic agents by reference to a result to be achieved. Consequently an opinion on novelty, inventive step and industrial applicability will only be given for those parts of the claims which appear clear, supported and the subject matter of which is disclosed in the description, namely those parts relating to the IFN-alpha therapeutic agents disclosed in the experimental section, examples 1-5.

Claims 1,3-13 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

- D1: ORTALDO J R ET AL: INTERNATIONAL JOURNAL OF CANCER, vol. 31, no. 3, 1983, pages 285-290.
- D2: PESTKA S: ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS. 15 FEB 1983, vol. 221, no. 1, 15 February 1983 (1983-02-15), pages 1-37.

- D3: SPERBER S J ET AL: JOURNAL OF INTERFERON RESEARCH, MARY ANN LIEBERT, INC., vol. 12, 1992, pages 363-368.
- D4: EVINGER M ET AL: ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, vol. 210, no. 1, 1981, pages 319-329.
- D5: WO 02 086156 A (ESCARY JEAN-LOUIS ;GENODYSSEE (FR)) 31 October 2002 (2002-10-31)
- D6: WO 02 079249 A (ESCARY JEAN-LOUIS ;GENODYSSEE (FR)) 10 October 2002 (2002-10-10)

1 The present application does not meet the requirements of Article 33(1) EPC, because the subject-matter of claims 14 is not new in the sense of Article 33(2) PCT.

1.1 D5 and D6 disclose natural allelic variants of IFN-alpha 17 and 21, respectively (see abstracts), therapeutic uses thereof, gene expression vectors comprising a polynucleotide encoding these polypeptides (D5, example 2, D6, example 3) and derivatives resulting from site directed mutagenesis (D5, page 13, lines 28-31; D6, page 14, line 31-page 15, line 2) comprising several natural genetic variations.

Therefore D5 and D6 anticipate independent claim 14.

1.2 D1 (abstract) discloses a method for providing new therapeutic agents comprising the following steps:

- selecting polypeptides encoded by a preselected gene member of a gene family with therapeutical potential (e.g. human IFN-alpha) or related genes thereof (human IFN-beta; human IFN-gamma)
- determining the therapeutic index of the polypeptides selected in step a (immunomodulatory activity vs. cytotoxicity ; Table 1, Figures 1-3).
- Retaining as a therapeutic agent the polypeptide selected in step a) whose therapeutic index as determined in step b), is higher than a therapeutic index of reference (e.g. IFN beta 2 vs. IFN beta 1; page 288, left-hand column, line 6-right-hand column, line 23). The assays are carried out without resorting to in vivo activity tests (i.e. on isolated monocytes).

The subject matter of independent claim 1 differs therefrom in that natural allelic variants of a polypeptide are selected in step a).

D2 discloses a similar method, involving antiviral and antiproliferative activity tests (page 23, right-hand column, line 14-page 26, right-hand column, line 14; Table VI). The same is disclosed for recombinant IFN variants (Table VII and VIII).

D3 and D4 disclose similar methods as D2.

Therefore, the novelty of independent claim 1 and dependent claims 2-13 is herewith acknowledged.

- 2 The present application does not meet the requirements of Article 33(1) PCT, because the subject-matter of claim 14 does not involve an inventive step in the sense of Article 33(2) PCT.
  - 2.1 Independent product claim 14 is manifestly not novel and there are no technical features that can be incorporated therein in order to render it inventive.
  - 2.2 As to claims 1-13, there is no suggestion in the prior art that natural allelic variants of therapeutic proteins can have an altered therapeutic efficiency, and therefore the selection protocol of claims 1-13 is *a priori* considered to involve an inventive step.
- 3 Claim 2 and 14 are considered to be industrially applicable in the sense of Article 33(4) PCT.
  - 3.1 For the assessment of the present claims 1,3-13 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.
- 4 The application does not meet the requirements of Article 6 PCT, because claims 1-14 are not clear.
  - 4.1 Present claims 1-14 involve the determination of the "therapeutic index". According to

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/EP 03/13695

the On-Line Medical Dictionary (<http://cancerweb.ncl.ac.uk>), the therapeutic index is "The ratio of LD50 to ED50, used in quantitative comparison of drugs". In the present application the "therapeutic index" has a somewhat different meaning and different way of calculation (page 11, lines 11-23; Examples 1-5), which is not clear from the wording of the claim alone.

In the present application "therapeutic indices" are determined by obtaining relative values of different activity tests (antiviral, antiproliferative, immunomodulatory and toxicity). The value of the toxicity test affected by a coefficient of 2/3 is subtracted from each of the three other activity test. Moreover in vitro and in vivo tests are involved that have different coefficients in the calculation of the "therapeutic index". All the details of this special way of determining the "therapeutical index" would need to be incorporated in independent claim 1 to render the claim clear.

What is claimed is:

1. A method for providing new therapeutic agent(s), characterized in that it comprises the following steps:
    - 5      a) selecting at least one polypeptide encoded by a natural allelic variant of one preselected gene with therapeutic potential;
    - b) determining the therapeutic index of the polypeptide(s) selected in step a) by
      - i) submitting the polypeptides selected in step a) to at least two activity tests;
      - ii) attributing a value to each polypeptide in direct relation with the results of 10      said activity tests; and
      - iii) determining the therapeutic index of each polypeptide from the values attributed in step ii).
    - c) retaining as therapeutic agent(s), the polypeptide(s) selected in step a) whose therapeutic index, as determined in step b), is higher than a 15      therapeutic index of reference.
  2. The method according to claim 1, wherein the therapeutic index in step b) is determined without resorting to *in vivo* activity tests.
  3. The method according to claim 1 or 2, characterized in that at least 2 polypeptides, preferably at least 4 polypeptides, are selected in step a).
  - 20      4. The method according to any one of claims 1 to 3, wherein the therapeutic index of reference is the therapeutic index of one reference product.
  5. The method according to any one of claims 1 to 4, characterized in that it further comprises a step d), wherein only the polypeptide(s) retained in step c) which has (have) the highest or second highest therapeutic index is (are) selected as 25      therapeutic agent(s).
- (introduced in step b) of claim 1)
6. The method according to any one of claims 3 to 5, wherein the polypeptides selected in step a) are polypeptides encoded by natural allelic variants of one preselected gene with therapeutic potential.
  - 30      7. The method according to any one of claims 1 to 6, wherein said natural allelic variants originate from the same species.
  8. The method according to claim 7, wherein said natural allelic variants originate from the human species

9. The method according to any one of claims 1 to 8, wherein the polypeptides selected in step a) are polypeptides encoded by natural allelic variants of one single gene that can be either the preselected gene with therapeutic potential or one related gene thereof.
- 5 10. The method according to any one of claims 1 to 9, wherein the polypeptides selected in step a) are under their mature form.
11. The method according to any one of claims 1 to 10, wherein the amino acid sequences of the mature form of all the polypeptides selected in step a) do not differ one from each other by more than 20 amino acids, preferably by more
- 10 12. The method according to any one of claims 1 to 11, wherein at least one activity test is carried out by means of a gene expression vector carrying a polynucleotide which encodes one of the polypeptides selected in step a).
- 15 13. The method according to any one of claims 1 to 12, wherein at least one activity test is carried out by means of a gene expression vector carrying a polynucleotide which encodes one of the polypeptides selected in step a).
14. A therapeutic agent obtainable by the method according to any one of claims 1 to 14.